

CLAIMS

What is claimed is:

1. An automated flinch-detection apparatus for measuring spatial displacement
5 of an animal's paw injected with irritant, comprising:

an electromagnetic detecting assembly having

a transmitting occilator for generating electrical current;

an electromagnetic transmitter coil coupled to the occilator for
generating an electromagnetic field;

10 an electromagnetic receiving coil placed in a linear plane directly
below the transmitter coil;

a first, receiving amplifier connected to the receiving coil;

an amplitude detector connected to the receiving amplifier;

a second amplifier connected to the amplitude detector;

15 a metal object attached to the animal's paw; and

a cylindrical observation chamber of a diameter not greater than the
diameter of the generated magnetic field, said chamber placed directly over the
receiving/transmitting coil assembly,

wherein the current generated by the transmitting occilator circulates in the
20 transmitter coil, creating an electromagnetic field that penetrates the metal object,
creating eddy currents perturbing the electromagnetic field, said fluctuating
perturbations being picked up by the receiving coil, amplified by the receiving
amplifier, detected by the amplitude detector and further amplified, filtered and
digitized.

25 2. The apparatus according to claim 1, wherein the current passing through the

transmitter coil generates an electromagnetic field in the 6 to 8 kilohertz range with a signal strength on the order of 5 to 8 milliwatts.

3. The apparatus according to claim 1, wherein the metal object to the animal's paw is a small metal annular collar.

4. The apparatus according to claim 1, wherein the metal object to the animal's paw is a small metal "C" collar in incomplete annular form.

5. The apparatus according to claim 1, wherein the metal object comprises a ferrous metal.

6. The apparatus according to claim 1, wherein the metal object comprises a non-ferrous metal.

7. The apparatus according to claim 1, wherein the observation chamber is a transparent cylindrical container, insuring that the animal will remain inside the boundaries of the electromagnetic field generated by the coil assembly.

8. The apparatus according to claim 1, wherein the observation chamber has individual compartments permitting testing of a plurality of animals.

9. The apparatus according to claim 1, wherein the detection assembly below the observation chamber has multiple independent detection units.

10. The apparatus according to claim 1, wherein the observation chamber is constructed of any rigid transparent plastic.

11. A method for measuring a flinch response by an animal whose paw has been subjected to an irritant, comprising:

attaching a metal object to the animal's paw;

5 placing the animal in an observation chamber situated directly over a detection assembly having

a transmitting occilator for generating electrical current,

an electromagnetic transmitter coil coupled to the occilator for generating an electromagnetic field;

10 an electromagnetic receiving coil that receives the generated electrical current;

a receiving amplifier that amplifies the received generated electrical current;

an amplitude detector; and

15 an amplifier for amplifying the amplitude detected,

wherein the current generated by the transmitting occilator circulates in the transmitter coil, creating an electromagnetic field that penetrates the metal object attached to the animal's paw, creating fluctuating eddy currents perturbing the electromagnetic field,

20 wherein said fluctuating perturbations are picked up by the receiving coil, amplified by the receiving amplifier, and detected by the amplitude detector, and wherein said pertubations are further amplified, filtered and digitized to produce a measured response to the irritant.

25 12. A method for measuring a flinch response to pain by an animal whose paw has been subjected to an irritant, comprising:

attaching a metal object to the animal's paw;

placing the animal in an observation chamber situated directly over a detection assembly;

generating electrical current by a transmitting occilator;

generating an electromagnetic field by an electromagnetic transmitter coil

5 coupled to the occilator;

receiving the generated electromagnetic field by a receiving coil;

amplifying the received generated electrical current by a receiving amplifier having,

an amplitude detector; and

10 an amplifier for amplifying the amplitude detected,

wherein the current generated by the transmitting occilator circulates in the transmitter coil, creating an electromagnetic field that penetrates the metal object attached to the animal's paw, creating fluctuating eddy currents perturbing the electromagnetic field,

15 wherein said fluctuating perturbations are picked up by the receiving coil, amplified by the receiving amplifier, and detected by the amplitude detector, and wherein said perturbations are further amplified, filtered and digitized to produce a measured response to the irritant.

REFERENCES

1. Abbadie, C., B. K. Taylor, M. A. Peterson, and A. I. Basbaum: Differential
5 contribution of the two phases of the formalin test to the pattern of c-fos expression
in the rat spinal cord: studies with remifentanil and lidocaine. *Pain* 69:101-10, 1997

2. Abbott, F. V., K. B. Franklin, and R. F. Westbrook: The formalin test:
scoring properties of the first and second phases of the pain response in rats. *Pain*
10 60:91-102, 1995

3. Abram, S. E., and T. L. Yaksh: Morphine, but not inhalation anesthesia,
blocks post-injury facilitation. The role of preemptive suppression of afferent
transmission. *Anesthesiology* 78:713-21, 1993
15

4. Abram, S. E., and T. L. Yaksh: Systemic lidocaine blocks nerve injury-
induced hyperalgesia and nociceptor-driven spinal sensitization in the rat.
Anesthesiology 80:383-91; discussion 25A, 1994

- 20 5. Aloisi, A. M., M. E. Albonetti, and G. Carli: Behavioural effects of
different intensities of formalin pain in rats. *Physiol Behav* 58:603-10, 1995

6. Bannon, A. W., M. W. Decker, P. Curzon, M. J. Buckley, D. J. Kim, R. J.
Radek, J. K. Lynch, J. T. Wasicak, N. H. Lin, W. H. Arnold, M. W. Holladay, M.
25 Williams, and S. P. Arneric: ABT-594 [(R)-5-(2-azetidylmethoxy)-2-
chloropyridine]: a novel, orally effective antinociceptive agent acting via neuronal
nicotinic acetylcholine receptors: II. In vivo characterization. *J Pharmacol Exp Ther*

285:787-94, 1998

7. Bhatnagar, S., M. F. Dallman, R. E. Roderick, A. I. Basbaum, and B. K. Taylor: The effects of prior chronic stress on cardiovascular responses to acute restraint and formalin injection. *Brain Research* 797:313-20, 1998

8. Brennan, T. J.: AMPA/kainate receptor antagonists as novel analgesic agents [editorial;comment]. *Anesthesiology* 89:1049-51, 1998

9. Buerkle, H., M. Marsala, and T. L. Yaksh: Effect of continuous spinal remifentanyl infusion on behaviour and spinal glutamate release evoked by subcutaneous formalin in the rat. *British Journal of Anaesthesia* 80:348-53, 1998

10. Chaplan, S. R., A. B. Malmberg, and T. L. Yaksh: Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. *Journal of Pharmacology and Experimental Therapeutics* 280:829-38, 1997

11. Clavelou, P., R. Dallel, T. Orliaguet, A. Woda, and P. Raboisson: The orofacial formalin test in rats: effects of different formalin concentrations. *Pain* 62:295-301, 1995

12.Coderre, T. J., M. E. Fundytus, J. E. McKenna, S. Dalal, and R. Melzack: The formalin test: a validation of the weighted-scores method of behavioural pain rating. *Pain* 54:43-50, 1993

13. Dallel, R., P. Raboisson, P. Clavelou, M. Saade, and A. Woda: Evidence

for a peripheral origin of the tonic nociceptive response to subcutaneous formalin.
Pain 61:11-6, 1995

14. Dickenson, A. H., L. C. Stanfa, V. Chapman, and T. L. Yaksh: Response
5 properties of dorsal horn neurons: Pharmacology of the dorsal horn, in Yaksh, T.
L., C. Lynch, III., W. M. Zapol, M. Maze, J. F. Biebuyck, and L. J. Saidman (eds)
Anesthesia: Biologic Foundations. Philadelphia: Lippincott-Raven Publishers,
1997, pp 611-624.

10 15. Dickenson, A. H., and A. F. Sullivan: Peripheral origins and central
modulation of subcutaneous formalin- induced activity of rat dorsal horn neurones.
Neurosci Lett 83:207-11, 1987

15 16. Dirig, D. M., and T. L. Yaksh: Intrathecal baclofen and muscimol, but not
midazolam, are antinociceptive using the rat-formalin model. *Journal of*
Pharmacology and Experimental Therapeutics 275:219-27, 1995

17. Dray, A., and A. Dickenson: Systemic capsaicin and olvanil reduce the
acute algogenic and the late inflammatory phase following formalin injection into
20 rodent paw. *Pain* 47:79-83, 1991

18. Dubuisson, D., and S. G. Dennis: The formalin test: a quantitative study of
the analgesic effects of morphine, meperidine, and brain stem stimulation in rats
and cats. *Pain* 4:161-74, 1977

25 19. Handwerker, H. O.: Electrophysiological mechanisms in inflammatory pain.
Agents and Actions. Supplements 32:91-9, 1991

20. Hunter, J. C., and L. Singh: Role of excitatory amino acid receptors in the mediation of the nociceptive response to formalin in the rat. *Neurosci Lett* 174:217-21, 1994
- 5 21. Jett, M. F., and S. Michelson: The formalin test in rat: validation of an automated system. *Pain* 64:19-25, 1996
22. Jourdan, D., D. Ardid, L. Bardin, M. Bardin, D. Neuzeret, L. Lanphouthacoul, and A. Eschalier: A new automated method of pain scoring in the formalin test in rats. *Pain* 71:265-70, 1997
- 10 23. Malmberg, A. B., M. F. Rafferty, and T. L. Yaksh: Antinociceptive effect of spinally delivered prostaglandin E receptor antagonists in the formalin test on the rat. *Neurosci Lett* 173:193-6, 1994
- 15 24. Malmberg, A. B., and T. L. Yaksh: Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *Journal of Pharmacology and Experimental Therapeutics* 263:136-46, 1992
- 20 25. Malmberg, A. B., and T. L. Yaksh: Pharmacology of the spinal action of ketorolac, morphine, ST-91, U50488H, and L-PIA on the formalin test and an isobolographic analysis of the NSAID interaction [see comments]. *Anesthesiology* 79:270-81, 1993
- 25 26. Malmberg, A. B., and T. L. Yaksh: Spinal nitric oxide synthesis inhibition blocks NMDA-induced thermal hyperalgesia and produces antinociception in the formalin test in rats. *Pain* 54:291-300, 1993

27. Malmberg, A. B., and T. L. Yaksh: Effect of continuous intrathecal infusion of omega-conopeptides, N-type calcium-channel blockers, on behavior and antinociception in the formalin and hot-plate tests in rats. *Pain* 60:83-90, 1995
- 5 28. Nozaki-Taguchi, N., and T. L. Yaksh: A novel model of primary and secondary hyperalgesia after mild thermal injury in the rat. *Neurosci Lett* 254:25-28, 1998
- 10 29. Peterson, M. A., A. I. Basbaum, C. Abbadie, D. S. Rohde, W. R. McKay, and B. K. Taylor: The differential contribution of capsaicin-sensitive afferents to behavioral and cardiovascular measures of brief and persistent nociception and to Fos expression in the formalin test. *Brain Research* 755:9-16, 1997
- 15 30. Prado, W. A., and A. S. Goncalves: Antinociceptive effect of intrathecal neostigmine evaluated in rats by two different pain models. *Braz J Med Biol Res* 30:1225-31, 1997
- 20 31. Price, D. D., G. J. Bennett, and A. Rafii: Psychophysical observations on patients with neuropathic pain relieved by a sympathetic block. *Pain* 36:273-88, 1989
- 25 32. Puig, S., and L. S. Sorkin: Formalin-evoked activity in identified primary afferent fibers: systemic lidocaine suppresses phase-2 activity. *Pain* 64:345-55, 1996
33. Raboisson, P., R. Dallel, P. Clavelou, B. J. Sessle, and A. Woda: Effects of subcutaneous formalin on the activity of trigeminal brain stem nociceptive

neurones in the rat. *Journal of Neurophysiology* 73:496-505, 1995

34. Shimoyama, N., M. Shimoyama, A. M. Davis, C. E. Inturrisi, and K. J. Elliott: Spinal gabapentin is antinociceptive in the rat formalin test. *Neurosci Lett* 222:65-7, 1997

35. Simmons, R. M., D. L. Li, K. H. Hoo, M. Deverill, P. L. Ornstein, and S. Iyengar: Kainate GluR5 receptor subtype mediates the nociceptive response to formalin in the rat. *Neuropharmacology* 37:25-36, 1998

36. Singh, L., M. J. Field, P. Ferris, J. C. Hunter, R. J. Oles, R. G. Williams, and G. N. Woodruff: The antiepileptic agent gabapentin (Neurontin) possesses anxiolytic- like and antinociceptive actions that are reversed by D-serine. *Psychopharmacology (Berl)* 127:1-9, 1996

37. Tallarida, R. J., and R. B. murray. *Manual of Pharmacologic Calculations With Computer Programs.* (2nd ed.) New York: Springer-Verlag, 1987:291.

38. Taylor, B. K., S. F. Akana, M. A. Peterson, M. F. Dallman, and A. I. Basbaum: Pituitary-adrenocortical responses to persistent noxious stimuli in the awake rat: endogenous corticosterone does not reduce nociception in the formalin test. *Endocrinology* 139:2407-13, 1998

39. Taylor, B. K., M. A. Peterson, and A. I. Basbaum: Persistent cardiovascular and behavioral nociceptive responses to subcutaneous formalin require peripheral nerve input. *Journal of Neuroscience* 15:7575-84, 1995

40. Taylor, B. K., M. A. Peterson, and A. I. Basbaum: Early nociceptive events influence the temporal profile, but not the magnitude, of the tonic response to subcutaneous formalin: effects with remifentanyl. *Journal of Pharmacology and Experimental Therapeutics* 280:876-83, 1997

5

41. Tjolsen, A., O. G. Berge, S. Hunskaar, J. H. Rosland, and K. Hole: The formalin test: an evaluation of the method [see comments]. *Pain* 51:5-17, 1992

10

42. Wheeler-Aceto, H., and A. Cowan: Standardization of the rat paw formalin test for the evaluation of analgesics. *Psychopharmacology* 104:35-44, 1991

43. Wheeler-Aceto, H., F. Porreca, and A. Cowan: The rat paw formalin test: comparison of noxious agents. *Pain* 40:229-38, 1990

15

44. Woolf, C. J.: Long term alterations in the excitability of the flexion reflex produced by peripheral tissue injury in the chronic decerebrate rat. *Pain* 18:325-43, 1984

20

45. Yaksh, T. L.: Preclinical models of nociception, in Yaksh, T. L., C. Lynch, III., W. M. Zapol, M. Maze, J. F. Biebuyck, and L. J. Saidman (eds) *Anesthesia: Biologic Foundations*. Philadelphia: Lippincott-Raven Publishers, 1997, pp 685-718. vol I).

25

46. Yaksh, T. L., D. H. Farb, S. E. Leeman, and T. M. Jessell: Intrathecal capsaicin depletes substance P in the rat spinal cord and produces prolonged thermal analgesia. *Science* 206:481-3, 1979

47. Yaksh, T. L., X. Y. Hua, I. Kalcheva, N. Nozaki-Taguchi, and M. Marsala: The spinal biology in humans and animals of pain states generated by persistent small afferent input. *Proceedings of the National Academy of Sciences of the United States of America* 96:7680-6, 1999

5

48. Yaksh, T. L., and A. B. Malmberg: Central pharmacology of nociceptive transmission, in Wall, P., and M. R. (eds) *Textbook of Pain*. 4th ed. Edinburgh, UK: Churchill Livingstone, 1999, pp 253-308.

10 49. Yaksh, T. L., and T. A. Rudy: Chronic catheterization of the spinal sub-arachnoid space. *Physiol Behav* 17:1031-1036, 1976

15 50. Yamamoto, T., and T. L. Yaksh: Stereospecific effects of a nonpeptidic NK1 selective antagonist, CP-96,345: antinociception in the absence of motor dysfunction. *Life Sci* 49:1955-63, 1991

51. Yoon, M. H., and T. L. Yaksh: The effect of intrathecal gabapentin on pain behavior and hemodynamics on the formalin test in the rat. *Anesthesia and Analgesia* 89:434-9, 1999

20

52. Zar, J. H. *Biostatistical Analysis*. (2nd ed.) Englewood Cliffs, NJ: Prentice-Hall, Inc., 1984

25